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(54) Title: DEPLETION OF E-ISOMERS IN PREPARATION OF Z-ENRICHED 3-(2-SUBSTITUTED VINYL) CEPHALOSPORINS

(57) Abstract: The present invention relates to depleting E-isomers of 3-(2-substituted vinyl) cephalosporins from a Z/E mixture of the same by selective crystallization techniques. The present invention to Z-enriched compounds comprising less than 5 % E-isomer.

DEPLETION OF E–ISOMERS IN PREPARATION OF Z-ENRICHED 3-(2-SUBSTITUTED VINYL) CEPHALOSPORINS

Field of Invention

The present invention relates to depleting E-isomers of 3-(2-substituted vinyl) cephalosporins from a Z/E mixture of the same by selective crystallization techniques. The present invention more specifically relates to Z-enriched compounds comprising less than 5 % E-isomer.

Background of Invention

Cephalosporin antibiotics belonging to the class of 3-(2-substituted vinyl) cephalosporins have a very broad spectrum of antimicrobial activity. Cefditoren pivoxil, which belongs to this class, is highly active not only against a variety of gram-positive and gram-negative bacteria, but also against some resistant strains of bacteria.

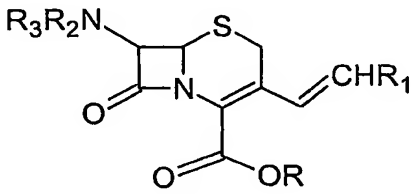
Cefditoren pivoxil is chemically described as [6R-[3(Z),6a,7b(Z)]]-7-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[2-(4-methyl-5-thiazolyl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-carboxylic acid, pivaloyloxymethyl ester. Due to the presence of vinyl group on the 3-position of the cephalosporin ring, cefditoren pivoxil is present in two isomeric forms, *viz.*, the E- or Z-isomeric forms. The antimicrobial activity, however, resides primarily in Z-isomer while the E-isomer exhibits no significant antimicrobial activity. Thus, efforts have concentrated on selectively removing the E-isomer, which might be generated during preparation of cefditoren.

European Patent No. 175610 discloses a process for preparing cefditoren and its pharmaceutically acceptable salts and esters. The disclosed process is non-selective and yields more than 20 % of the undesirable E-isomer, which is then tediously separated by column chromatography. The overall yield of cefditoren, its sodium salt or its pivaloxymethyl ester is reportedly very low.

U.S. Patent No. 6,288,223 discloses a process for the selective preparation of Z-isomer of 3-2-(substituted vinyl)cephalosporins. In this process, the reaction condition, as well as solvent system, is selected so that the Z-isomer is selectively obtained without the formation of the E-isomer during the formation of the vinyl group. The process, however, generates about 4 to 5 % of the unwanted E-isomer while requiring separation to obtain

the desired purity of the finished product. In addition, it gives a low yield of cefditoren pivoxil.

U.S. Patent No. 5,616,703 discloses a process for the separation of cephalosporin isomers by forming amine salts. The disclosed process produces the intermediate 7-ATCA of Formula I,



FORMULA I

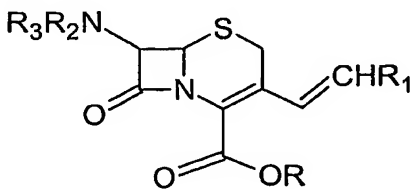
wherein R, R_2 and R_3 are hydrogen and R_1 is 5-methylthiazolyl group, and having a content of more than 20 % of the unwanted E-isomer, which isomer is depleted by forming amine salts. In this process, the amine salt of 7-ATCA is isolated, crystallized to selectively separate the E-isomer, and the Z-isomer enriched amine salt is then converted back to free 7-ATCA. Subsequent conversion of this intermediate to cephalosporin antibiotic is, however, not exemplified in this patent.

PCT Patent Publication WO 05/016936 discloses processes for selective preparation of the Z-isomer of cefditoren or pharmaceutically acceptable salts and esters thereof. The processes selectively prepare the Z-isomer of cefditoren pivoxil having less than 1 % of the E-isomer.

However, there remains a need for effective methods for selectively obtaining Z-isomers of cefditoren.

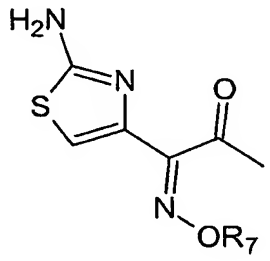
Summary of Invention

Provided herein are processes for depleting E-isomers of 3-(2-substituted vinyl)cephalosporin compounds of Formula I from Z/E mixtures thereof,



FORMULA I

wherein R can be a hydrogen atom, esterifying residue or a metal cation capable of forming a salt; R_1 can be hydrogen or a 5-, 6- or 7-membered heterocyclic residue comprising one or more heteroatoms selected from N, S or O, halo, substituted C_{1-8} alkyl, aryl, aralkyl, or SR_6 wherein R_6 is straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl, or a heterocyclic residue; and R_2 and R_3 are independently hydrogen, monovalent amino protecting group or a group of Formula A,



FORMULA A

wherein R_7 can be lower alkyl or R_2 and R_3 together form a divalent amino protecting group,

wherein the processes comprise the steps of:

a) treating Z/E mixture of compounds of Formula I having unwanted E-isomers with one or more amines, wherein R is hydrogen or a metal cation capable of forming a salt;

b) adding one or more salt forming agents; and

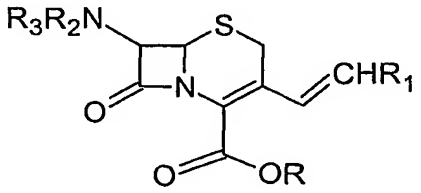
c) isolating a Z-enriched compound of Formula I.

The processes can include one or more of the following embodiments. For example, the amines can be selected from compounds of Formula $NR_4R_5R_6$, wherein R_4, R_5 and R_6 can be independently hydrogen, C_{1-6} straight or branched chain alkyl, C_{3-10} single or fused ring cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, or independently R_3, R_4 and R_5 can combine with each other to form a C_{3-7} cycloalkyl or heterocyclic residue comprising one or more heteroatoms selected from S, N or O. In particular, the amines can selected from methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, cyclopropylamine, cyclobutylamine, cyclopentylamine, cyclohexylamine, dicyclohexylamine, cycloheptylamine, aniline, N-methylaniline, N,N-dimethylaniline, p-toluidine, p-nitroaniline, diphenylamine,

morpholine, N-methylmorpholine, piperazine, piperidine, N-methylpiperidine, pyrrolidine, N-methylpyrrolidine, N-methylpiperazine or mixtures thereof.

In another embodiment, the salt forming agents can be selected from sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium methoxide, sodium ethoxide, sodium 2-ethylhexanoate, potassium hydroxide, potassium carbonate, potassium t-butoxide, potassium acetate or mixtures thereof. In yet another embodiment, the processes can further comprise converting Z-enriched compounds of Formula I to its pharmaceutically acceptable esters by treating Z-enriched compounds of Formula I with one or more compounds of Formula R-L, wherein R comprises a C_{1-10} alkyl, 1-alkanoyloxyalkyl, 1-alkoxycarbonyloxyalkyl, cycloalkyl, cycloalkyloxy or C_{1-10} alkoxy and L is a leaving group. The compounds of Formula R-L can be selected from iodomethyl pivalate, bromomethyl pivalate, acetoxyethyl bromide, cyclohexyloxycarbonate, cyclohexyloxy-1-methylethylcarbonate or mixtures thereof.

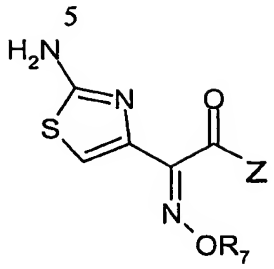
Also provided herein are processes for depleting E-isomers of 3-(2-substituted vinyl)cephalosporin compounds of Formula I from Z/E mixtures thereof,



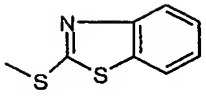
FORMULA I

wherein the processes comprise the steps of:

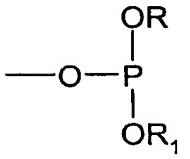
a) reacting Z/E/ mixtures of compounds of Formula I, wherein R can be a hydrogen atom, esterifying residue or a metal cation capable of forming a salt, with one or more compounds of Formula II, wherein Z can be selected from a group having Formula IIa, IIb, IIc, IId; and R, R_2 and R_3 can independently be hydrogen,



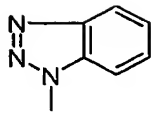
FORMULA II



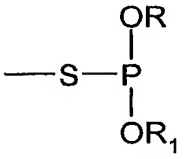
FORMULA IIa



FORMULA IIb



FORMULA IIc



FORMULA IId

b) optionally isolating Z/E mixtures of compounds of Formula I, wherein one of R_2 and R_3 can be hydrogen and the other of R_2 and R_3 can be a group of Formula A, wherein R_7 can be lower alkyl;

c) optionally treating products obtained in step a) or b) with one or more amines;

d) adding one or more salt forming agents; and

e) isolating Z-enriched compounds of Formula I.

Such processes can include one or more of the following embodiments. For example, the compounds of Formula II can be selected from 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, benzotriazol-1-yl ester; 2-methoxyimino-2-(2-aminothiazol-4-yl)acetic acid, S-2-benzothiazole ester; 2-methoxyimino-2-(2-aminothiazol-4-yl)acetic acid, dialkylphonate ester or diarylphosphonate ester; 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, dialkylphosphothionate ester, diarylphosphothionate ester or mixtures thereof. In another embodiment, Z/E mixtures of compounds of Formula I can be isolated in step b).

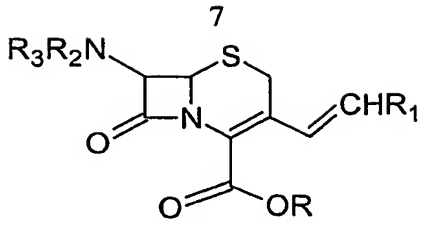
In one embodiment, the amines can be selected from compounds of Formula $NR_4R_5R_6$, wherein R_4, R_5 and R_6 can be independently selected from hydrogen, C_{1-6} straight or branched chain alkyl, C_{3-10} single or fused ring cycloalkyl, optionally substituted aryl, optionally substituted aralkyl or independently R_3, R_4 and R_5 combine with each other to form a C_{3-7} membered cycloalkyl or heterocyclic residue containing one or more heteroatoms selected from S, N or O. Particular amines can be selected from methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, cyclopropylamine, cyclobutylamine, cyclopentylamine, cyclohexylamine, dicyclohexylamine, cycloheptylamine, aniline, N-methylaniline, N,N-dimethylaniline, p-toluidine, p-nitroaniline, diphenylamine, morpholine, N-methylmorpholine, piperazine, piperidine, N-methylpiperidine, pyrrolidine, N-methylpyrrolidine, N-methylpiperazine or mixtures thereof.

In another embodiment, salt forming agents can be selected from sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium methoxide, sodium ethoxide, sodium 2-ethylhexanoate, potassium hydroxide, potassium carbonate, potassium t-butoxide, potassium acetate or mixtures thereof.

In another embodiment, the processes can further comprise converting Z-enriched compounds of Formula I to its pharmaceutically acceptable esters by treating Z-enriched compounds of Formula I with one or more compounds of Formula R-L, wherein R comprises an alkyl, 1-alkanoyloxyalkyl, 1-alkoxycarbonyloxyalkyl, cycloalkyl, cycloalkyloxy or alkoxy, having 1 to 10 carbon atoms and L is a leaving group. Particular compounds of Formula R-L can be selected from iodomethyl pivalate, bromomethyl pivalate, acetoxyethyl bromide, cyclohexyloxycarbonate, cyclohexyloxy-1-methylethylcarbonate or mixtures thereof.

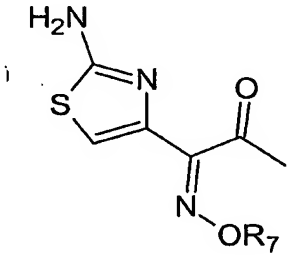
In another embodiment, reaction of step a) can be carried out in the presence of one or more bases, wherein the one or more bases can be selected from one or more inorganic compounds or one or more organic salts. Particular bases can be selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, aluminum hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium methoxide, potassium t-butoxide, sodium ethoxide, triethylamine, dicyclohexylamine, diphenylamine or mixtures thereof.

Also provided herein are Z-enriched compounds of Formula I,



FORMULA I

wherein R can be a hydrogen atom, esterifying residue or a metal cation capable of forming a salt; R_1 can be hydrogen or a 5, 6 or 7 membered heterocyclic residue containing one more heteroatoms selected from N, S or O, halo, substituted C_{1-8} alkyl, aryl, aralkyl, or SR_6, wherein R_6 can be straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl, or a heterocyclic residue; and R_2 and R_3 can independently be hydrogen, monovalent amino protecting group or a group of Formula A,



FORMULA A

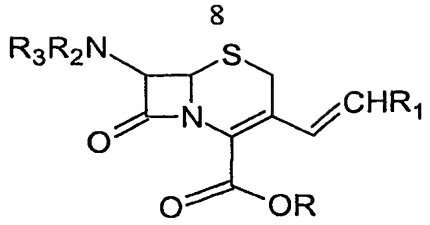
wherein R_7 can be lower alkyl or R_2 and R_3 can together form a divalent amino protecting group, comprising less than 5% of unwanted E-isomer.

In one embodiment, Z-enriched compounds of Formula I comprise less than 2 % E-isomers. In other embodiments, Z-enriched compounds of Formula I comprise less than 0.5% E-isomers.

Detailed Description of the Invention

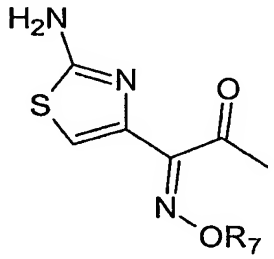
The present invention relates to selective depletion of E-isomers of 3-(2-substituted vinyl) cephalosporins from a mixture of Z/E isomers by selective crystallization techniques, for example, by *in situ* formation of the salt of cephalosporin compound. Typically, the formation of such salt of 3-(2-substituted vinyl) cephalosporins results in less than 2 % of unwanted E-isomers.

The term "Z-enriched compound of Formula I," unless otherwise specified, refers to compounds of Formula I having less than 5 % of unwanted E-isomer present,



FORMULA I

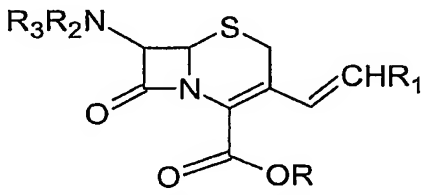
wherein R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt; R_1 is hydrogen or a 5-, 6- or 7-membered heterocyclic residue comprising one more heteroatoms selected from N, S or O, halo, substituted C_{1-8} alkyl, aryl, aralkyl, or SR_6 wherein R_6 is straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl, or a heterocyclic residue; and R_2 and R_3 are independently hydrogen, monovalent amino protecting group, a group of Formula A,



FORMULA A

wherein R_7 is lower alkyl, or R_2 and R_3 together form a divalent amino protecting group. More preferably, the unwanted E-isomer is present at less than 2 %, and most preferably the unwanted E-isomer is present at less than 0.5%. The term also encompasses pharmaceutically or physiologically acceptable salts, crystalline forms, solvates, hydrates, or amorphous forms of compounds of Formula I.

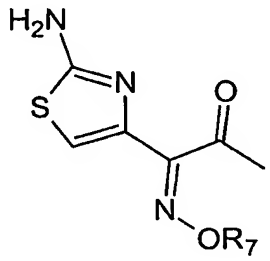
The term "Z/E mixture of compounds of Formula I," unless otherwise specified, refers to compounds of Formula I,



FORMULA I

wherein R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt; R_1 is hydrogen or a 5-, 6- or 7-membered heterocyclic residue comprising one or more heteroatoms

selected from N, S or O, halo, substituted C_{1-8} alkyl, aryl, aralkyl, or SR_6 wherein R_6 is straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl, or a heterocyclic residue; and R_2 and R_3 are independently hydrogen, monovalent amino protecting group, a group of Formula A,



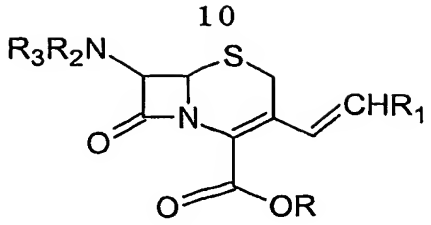
FORMULA A

wherein R_7 is lower alkyl, or R_2 and R_3 together form a divalent amino protecting group, which has more than 5% of unwanted E-isomer present in it. More preferably the unwanted E-isomer is more than 10% and most preferably the unwanted E-isomer is less than 20%. The term encompasses pharmaceutically or physiologically acceptable salts, crystalline forms, solvates, hydrates, or amorphous form of compound of Formula I.

A term "amine," unless otherwise specified, refers to a compound of Formula $NR_4R_5R_6$ wherein R_4, R_5 and R_6 are independently selected from hydrogen, C_{1-6} straight or branched chain alkyl, C_{3-10} single or fused ring cycloalkyl, optionally substituted aryl, optionally substituted aralkyl or independently R_3, R_4 and R_5 can combine with each other to form a C_{3-7} membered cycloalkyl or heterocyclic residue containing one or more heteroatoms selected from S, N or O.

A term "salt forming agent," unless otherwise specified, refers to a compound containing a metal cation capable of forming salt, which can be selected from alkali or alkaline earth metal hydroxides, hydrides, carbonates, bicarbonates, alkoxides wherein the alkoxide residue contains C_{1-10} straight or branched chain alkyl group, carboxylates wherein the carboxylic residue contains C_{1-25} straight or branched chain alkyl group.

Accordingly, provided herein are processes for depleting E-isomers of 3-(2-substituted vinyl)cephalosporin compounds of Formula I



FORMULA I

from a Z/E mixture thereof, wherein the processes comprise the steps of:

a) forming a reaction mixture by treating a Z/E mixture of a compound of Formula I having unwanted E-isomer, wherein R is hydrogen or a metal cation capable of forming a salt, with one or more amines;

b) adding one or more salt forming agents to the reaction mixture; and

c) isolating a Z-enriched compound of Formula I.

Z/E mixtures of a compound of Formula I having unwanted E-isomer impurity, wherein R is hydrogen or a metal cation capable of forming a salt, can be suspended in one or more organic solvents optionally containing water and one or more amines can be added to the suspension to dissolve the solids completely to form a solution. One or more salt forming agents can be added to the solution, either as such or in a form of a solution in the same organic solvent(s), and salts of compounds of Formula I precipitate out from the reaction mixture, which then can be isolated by filtration. The solid can be washed with the same organic solvent(s) and dried to obtain a Z-enriched compound of Formula I in salt form, wherein R is a metal cation, which can be further converted to a compound of Formula I, wherein R is hydrogen. Compounds of Formula I, wherein R is hydrogen or a metal cation capable of forming a salt, can be treated with compounds having the Formula R-L, wherein R can be an esterifying residue and L can be a leaving group, to subsequently convert R to an esterifying residue.

Suitable organic solvents can be one or more polar aprotic solvents, for example, dimethylformamide, dimethylacetamide, dimethylsulphoxide, dioxane, tetrahydrofuran, acetone, acetonitrile; one or more polar protic solvents, for example, methanol, ethanol, isopropanol, n-propanol, n-butanol, t-butanol or other alcohols; esters, for example, ethyl acetate, methyl acetate, ethyl formate; or mixtures thereof.

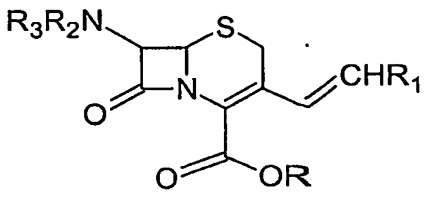
Examples of amines of Formula $NR_4R_5R_6$ include, but are not limited to, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, cyclopropylamine,

cyclobutylamine, cyclopentylamine, cyclohexylamine, dicyclohexylamine, cycloheptylamine, aniline, N-methylaniline, N,N-dimethylaniline, p-toluidine, p-nitroaniline, diphenylamine, morpholine, N-methylmorpholine, piperazine, piperidine, N-methylpiperidine, pyrrolidine, N-methylpyrrolidine, N-methylpiperazine or mixtures thereof.

Examples of salt forming agents include, but are not limited to, sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium methoxide, sodium ethoxide, sodium 2-ethylhexanoate, potassium hydroxide, potassium carbonate, potassium t-butoxide, potassium acetate, and the like, or mixtures thereof.

The Z-enriched compound of Formula I, wherein R is hydrogen or a metal cation capable of forming a salt, can be further subjected to the above-described process to further deplete unwanted E-isomer such that the unwanted E-isomer can be present at less than 0.5.

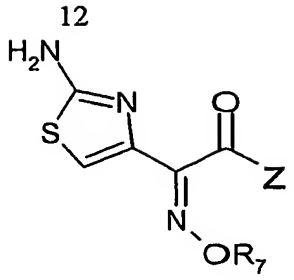
A second aspect of the present invention provides for processes for depleting E-isomers of 3-(2-substituted vinyl) cephalosporin compounds of Formula I,



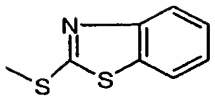
FORMULA I

wherein the processes comprise the steps of:

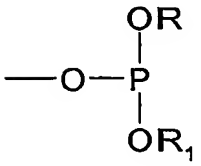
a) reacting a Z/E mixture of a compound of Formula I with a compound of Formula II, wherein Z is selected from Formula IIa, IIb, IIc, or IId and R, R_2 and R_3 are hydrogen;



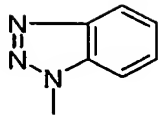
FORMULA II



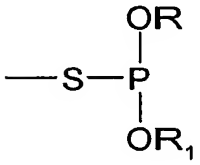
FORMULA IIa



FORMULA IIb



FORMULA IIc



FORMULA IId

b) optionally isolating compounds of Formula I, wherein one of R_2 or R_3 is hydrogen and the other of R_2 or R_3 is a group of Formula A, wherein R_7 is lower alkyl, and the compound of Formula I is a Z/E mixture;

c) if required, treating the compounds obtained in step a) or b) with one or more amines;

d) adding one or more salt forming agents; and

e) isolating Z-enriched compounds of Formula I.

The reaction of step a) can be carried out in presence of one or more organic solvents optionally containing water and one or more bases at a temperature of about -50 °C to 60 °C to form compounds of Formula I.

The compound of Formula II can be selected from 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, benzotriazol-1-yl ester; 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, S-2-benzothiazole ester; 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, dialkylphonate ester or diarylphosphonate ester; 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, dialkylphosphothionate ester or diarylphosphothionate ester.

Suitable solvents in step a) can be selected from chlorinated hydrocarbons, *e.g.*, methylene chloride, chloroform, ethylene chloride, ethylene bromide or mixtures thereof; ethers, *e.g.*, tetrahydrofuran, diethyl ether or mixtures thereof; ketones, *e.g.*, acetone, methyl isobutyl ketone, methyl ethyl ketone or mixtures thereof; alcohols, *e.g.*, methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof; or mixtures thereof. Such suitable solvents can also optionally contain water.

Suitable bases can be one or more inorganic compounds, *e.g.*, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, aluminum hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate; and/or one or more organic salts, *e.g.*, sodium methoxide, potassium t-butoxide, sodium ethoxide, or organic ammonium compounds such as triethylamine, dicyclohexylamine, diphenylamine or mixtures thereof.

After preparing a solution of a Z/E mixture of a compound of Formula I and a compound of Formula II, wherein R is hydrogen and both R_2 and R_3 and compound of Formula II, in a suitable mixture of solvents, one or more bases can be added slowly. After the reaction is completed, dichloromethane can be added to quench the reaction and the aqueous and non-aqueous layers can be separated.

The aqueous layer can be acidified using one or more suitable mineral acids to adjust the pH to a range of about 4.5 to about 5. The Z/E mixture of compounds of Formula I, wherein one of the R_2 and R_3 is hydrogen and the other of R_2 and R_3 is a group of Formula A, wherein R_7 is lower alkyl, precipitate out and can then be filtered.

Alternatively, one or more amines are added to the aqueous layer as obtained above if the base in step a) is not one or more organic ammonium compounds. Accordingly, the addition of amines is not required if organic ammonium compounds are used as a base in step a). One or more salt forming agents can be added to the solution, either as such or in the form of a solution in the same organic solvent(s) and a precipitate that forms can be filtered from the reaction mixture. The solid can be washed with the same organic solvent(s) and then dried to obtain a salt of the Z-enriched compound of Formula I, wherein R is a metal cation, which can be further converted to a compound of Formula I, wherein R is hydrogen. Compounds of Formula I, wherein R is hydrogen or a metal cation capable of forming a salt, can be treated with compounds having the Formula R-L,

wherein R can be an esterifying residue and L can be a leaving group, to subsequently convert R to an esterifying residue.

The Z–enriched compound of Formula I, wherein R is hydrogen or a metal cation capable of forming a salt, can be further subjected to the above-described process to further deplete unwanted E-isomer such that the unwanted E-isomer can be present at less than 0.5 %.

A third aspect of the present invention provides for Z-enriched compounds of Formula I, wherein R is a physiologically hydrolysable ester selected from alkyl, 1-alkanoyloxyalkyl, 1-alkoxycarbonyloxyalkyl, cycloalkyl, cycloalkyloxy or alkoxy, having 1 to 10 carbon atoms, wherein the process comprises the steps of: reacting a Z-enriched compound of Formula I, wherein R is hydrogen or a metal cation capable of forming a salt, with one or more compounds of Formula R-L, wherein R is a physiologically hydrolysable ester residue as mentioned above and L is a leaving group.

Compounds of Formula R-L can be selected from compounds, wherein R comprises an alkyl, 1-alkanoyloxyalkyl, 1-alkoxycarbonyloxyalkyl, cycloalkyl, cycloalkyloxy or alkoxy, having 1 to 10 carbon atoms and L is leaving group. Examples of compounds of Formula R-L include, but are not limited to, iodomethyl pivalate, bromomethyl pivalate, acetoxyethyl bromide, cyclohexyloxycarbonate, cyclohexyloxy-1-methylethylcarbonate and the like or mixtures thereof.

The reaction can be conveniently carried out in presence of one or more organic solvents selected from polar aprotic solvents, *e.g.*, dimethylsulphoxide, dimethylacetamide, dimethylformamide, 1,4-dioxane, tetrahydrofuran and the like or mixtures thereof. Reaction temperatures can be between about –25 °C to about 75 °C, depending on the nature of compound of Formula R-L and its reactivity.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

Examples

EXAMPLE 1 Depletion of E-isomer of Cefditoren acid (Compound of Formula I wherein R is H, R_1 is 4-methyl-thiazol-5-yl and R_2 is compound of Formula A wherein R_7 is methyl)

Step A: Preparation of Z-enriched potassium salt of cefditoren

Triethylamine (1.0 g) was added slowly to a stirred mixture of cefditoren acid (1.5 g, E-isomer = 22 %) in aqueous acetone (15 mL) at ambient temperature. Potassium acetate (0.38 g) was added to the reaction mixture and the reaction mixture was stirred for 3 to 4 hours during which the potassium salt of cefditoren began separating out. An additional quantity of acetone (35 mL) was added and the reaction mass was further stirred for an additional 3 to 4 hours. The resulting solid was filtered under vacuum, washed with acetone and air dried to yield a Z-enriched potassium salt of cefditoren acid (1.0 g).

HPLC Purity (% area)

Cefditoren-K (Z-isomer): 98.2

Cefditoren-K (E-isomer): 1.72

Step B: Preparation of Z-enriched cefditoren acid

The potassium salt of cefditoren obtained from Step A was dissolved in deionized water and the pH was adjusted to about 2.8 to 3.0. The separated solids were filtered and washed with deionized water to yield the title compound.

HPLC Purity (% area)

Cefditoren acid (Z-isomer): 98.2

Cefditoren acid (E-isomer): 1.72

EXAMPLE 2 Depletion of E-isomer of Cefditoren acid (Compound of Formula I wherein R is H, R_1 is 4-methyl-thiazol-5-yl and R_2 is compound of Formula A wherein R_7 is methyl)

Step A: Preparation of Z-enriched sodium salt of cefditoren

Triethylamine (1.0 g) was added slowly to a stirred mixture of cefditoren acid (5.0 g, E-isomer = 22%) in aqueous acetone (50 mL) at ambient temperature. Sodium 2-ethylhexanoate (2.0 g) was added to the reaction mixture and the reaction mixture was stirred for 3 to 4 hours during which the sodium salt of cefditoren began separating out. An additional quantity of acetone (100 mL) was added and the reaction mixture was stirred for an additional 3 to 4 hours. The resulting

solid was filtered under vacuum, washed with acetone and air dried to yield a Z-enriched sodium salt of cefditoren acid (3.4 g).

HPLC Purity (% area)

Cefditoren-Na (Z-isomer): 98.5

Cefditoren-Na (E-isomer): 1.41

Step B: Preparation of Z-enriched cefditoren acid

Cefditoren acid was obtained as per the process exemplified in Example 1. The sodium salt of cefditoren obtained as per Step A of Example 2 was dissolved in deionized water and the pH was adjusted to about 2.8 to 3.0. The separated solids were filtered and washed with deionized water to yield the title compound.

HPLC Purity (% area)

Cefditoren acid (Z-isomer): 98.5

Cefditoren acid (E-isomer): 1.41

EXAMPLE 3 Depletion of E-isomer of Cefditoren acid (Compound of Formula I wherein R is H, R_1 is 4-methyl-thiazol-5-yl and R_2 is compound of Formula A wherein R_7 is methyl)

Step A: Preparation of Z-enriched sodium salt of cefditoren

Triethylamine (0.2 g) was added slowly to a stirred mixture of cefditoren acid (1.0 g, E-isomer = 13.4%) in aqueous acetone (10 mL) at ambient temperature. Sodium 2-ethylhexanoate (0.4 g) was added to the reaction mixture and the reaction mixture was stirred for 3 to 4 hours during which the sodium salt of cefditoren began separating out. An additional quantity of acetone (20 mL) was added and the reaction mixture was stirred for an additional 3 to 4 hours. The resulting solid was filtered under vacuum, washed with acetone and air dried to yield a Z-enriched cefditoren sodium salt (0.71g).

HPLC Purity (% area)

Cefditoren-Na (Z-isomer): 98.7

Cefditoren-Na (E-isomer): 1.29

Step B: Preparation of Z-enriched cefditoren acid

Cefditoren acid was obtained as per the process exemplified in Example 1. The sodium salt of cefditoren obtained as per Step A of Example 3 was dissolved in deionized water and the pH was adjusted to about 2.8 to 3.0. The separated solids were filtered and washed with deionized water to yield the title compound.HPLC Purity (% area)

Cefditoren acid (Z-isomer): 98.7

Cefditoren acid (E-isomer): 1.29

EXAMPLE 4 Depletion of E-isomer of Cefditoren acid (Compound of Formula I wherein R is H, R_1 is 4-methyl-thiazol-5-yl and R_2 is compound of Formula A wherein R_7 is methyl)

Step A: Preparation of Z-enriched sodium salt of cefditoren

Triethylamine (1.0 g) was added slowly to a stirred mixture of cefditoren acid (5.0 g, E-isomer = 1.87%) in aqueous acetone (30 mL) at ambient temperature. Sodium 2-ethylhexanoate (2.0 g) was added to the reaction mixture and the reaction mixture was stirred for 3 to 4 hours during which the sodium salt of cefditoren began separating out. An additional quantity of acetone (20 mL) was added and the reaction mixture was stirred for an additional 3 to 4 hours. The resulting solid was filtered under vacuum, washed with acetone and air dried to yield a Z-enriched cefditoren sodium salt (4.35 g).

HPLC Purity (% area)

Cefditoren-Na (Z-isomer): 99.62

Cefditoren-Na (E-isomer): 0.32

Step B: Preparation of Z-enriched cefditoren acid

Cefditoren acid was obtained as per the process exemplified in Example 1. The sodium salt of cefditoren obtained as per Step A of Example 4 was dissolved in deionized water and the pH was adjusted to about 2.8 to 3.0. The separated solids were filtered and washed with deionized water to yield the title compound.

HPLC Purity (% area)

Cefditoren acid (Z-isomer): 99.62

Cefditoren acid (E-isomer): 0.32

EXAMPLE 5 Depletion of E-isomer of Cefditoren acid (Compound of Formula I wherein R is H, R_1 is 4-methyl-thiazol-5-yl and R_2 is compound of Formula A wherein R_7 is methyl)

Step A: Preparation of Z-enriched sodium salt of Cefditoren from 7-amino-3-[2-(4-methyl-5-thiazolyl)vinyl]-3-cephem-4-carboxylic acid

2-methoxyimino-2-(2-aminothiazol-4-yl)acetic acid, S-2-benzothiazole ester (3.25 g) was added to a stirred mixture of 7-amino-3-[2-(4-methyl-5-thiazolyl)vinyl]-3-cephem-4-carboxylic acid (2.5 g, E-isomer = 5.26%) in aqueous acetone (30 mL) at 0 °C to 5 °C, followed by slow addition of triethylamine (0.82 g) over 10 to 15 min. The reaction mixture was stirred at 10 °C to 15 °C for 3 to 4 hours. After completion of the reaction, the reaction mixture was quenched by adding dichloromethane (100 mL) and the resulting layers were separated. The aqueous layer was washed with dichloromethane (25 mL). Acetone (12.5 mL) was added to the aqueous layer followed by addition of sodium 2-ethylhexanoate (1.54 g). The mixture was stirred for an hour at 20 °C to 25 °C. An additional quantity of acetone (50 mL) was added to complete the crystallization. The resulting solid was filtered under vacuum, washed with acetone and dried to yield 2.9 g of a Z-enriched cefditoren sodium salt.

HPLC Purity (% area)

Cefditoren-Na (Z-isomer): 98.8

Cefditoren-Na (E-isomer): 1.14

Step B: Preparation of Z-enriched cefditoren acid

Cefditoren acid was obtained as per the process exemplified in Example 1. The sodium salt of cefditoren obtained as per Step A of Example 5 was dissolved in deionized water and the pH was adjusted to about 2.8 to 3.0. The separated solids were filtered and washed with deionized water to yield the title compound.

HPLC Purity (% area)

Cefditoren acid (Z-isomer): 98.8

Cefditoren acid (E-isomer): 1.14

EXAMPLE 6 Depletion of E-isomer of Cefditoren acid (Compound of Formula I wherein R is H, R_1 is 4-methyl-thiazol-5-yl and R_2 is compound of Formula A wherein R_7 is methyl)

Step A: Preparation of Z-enriched sodium salt of Cefditoren from 7-amino-3-[2-(4-methyl-5-thiazolyl)vinyl]-3-cephem-4-carboxylic acid

2-methoxyimino-2-(2-aminothiazol-4-yl)acetic acid, S-2-benzothiazole ester (19.5 g) was added to a stirred mixture of 7-amino-3-[2-(4-methyl-5-thiazolyl)vinyl]-3-cephem-4-carboxylic acid (15 g, E-isomer = 7.5%) in aqueous acetone (30 mL) at 0 °C to 5 °C, followed by slow addition of triethylamine (4.97 g) over 10 to 15 minutes. The reaction mixture was stirred at 10 °C to 15 °C for 3 to 4 hours. After completion of the reaction, the reaction mixture was quenched by adding dichloromethane (150 mL) and the resulting layers were separated. The aqueous layer was washed with dichloromethane (100 mL). Acetone (300 mL) was added to the aqueous layer followed by addition of sodium 2-ethylhexanoate (9.2 g). The mixture was stirred for an hour at 20 °C to 25 °C. An additional quantity of acetone (300 mL) was added to complete the crystallization. The resulting solid was filtered under vacuum, washed with acetone and dried to yield 18.0 g of a Z-enriched cefditoren sodium salt.

HPLC Purity (% area)

Cefditoren-Na (Z-isomer): 98.7

Cefditoren-Na (E-isomer): 1.27

Step B: Preparation of Z-enriched cefditoren acid

Cefditoren acid was obtained as per the process exemplified in Example 1. The sodium salt of cefditoren obtained as per Step A of Example 6 was dissolved in deionized water and the pH was adjusted to about 2.8 to 3.0. The separated solids were filtered and washed with deionized water to yield the title compound..

HPLC Purity (% area)

Cefditoren acid (Z-isomer): 98.7

Cefditoren acid (E-isomer): 1.27

EXAMPLE 7 Preparation of Z-enriched Cefditoren pivoxil

A sodium salt of cefditoren obtained in Example 6, Step B (10 g) was dissolved in DMF (60 mL) and cooled to about –15 °C. Iodomethyl-pivalate (5 g) was added in one lot to the reaction mixture at –15 °C. The reaction mixture was stirred at –10 °C to –15 °C for one hour. After completion of the reaction, the reaction mixture was quenched by adding a pre-cooled mixture of ethyl acetate and deionized water. The resulting layers were separated and the ethyl acetate layer was washed twice by water followed by carbon (charcoal) treatment. After filtering the ethyl acetate layer to remove carbon (charcoal), the ethyl acetate layer was concentrated under reduced pressure until the residual volume was about 40 to 45 mL. The resulting concentrated solution was added dropwise to cyclohexane (300 mL) at a temperature of 20 °C to 25°C. The separated solid was filtered and washed with cyclohexane to yield crude cefditoren pivoxil (10 g).

Crude cefditoren pivoxil (10 g) was purified by suspending the crude cefditoren pivoxil in denatured spirit (100 mL) at 20 °C to 25 °C for two hours. The resulting solid was filtered under vaccum and washed with DNS to yield pure Cefditoren pivoxil (7.0 g).

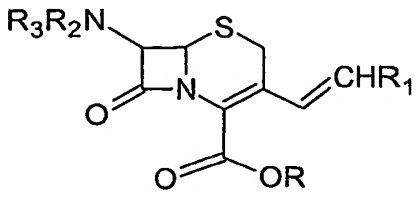
HPLC Purity (% area)

Cefditoren pivoxil (Z-isomer): 99.6

Cefditoren pivoxil (E-isomer): 0.37

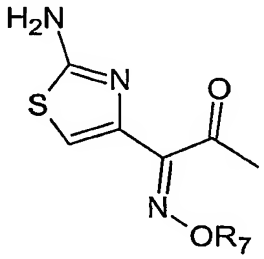
We claim:

1. A process for depleting E-isomers of a 3-(2-substituted vinyl)cephalosporin compound of Formula I from a Z/E mixture thereof,



FORMULA I

wherein R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt; R_1 is hydrogen or a 5-, 6- or 7-membered heterocyclic residue comprising one or more heteroatoms selected from N, S or O, halo, substituted C_{1-8} alkyl, aryl, aralkyl, or SR_6 wherein R_6 is straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl, or a heterocyclic residue; and R_2 and R_3 are independently hydrogen, monovalent amino protecting group or a group of Formula A,



FORMULA A

wherein R_7 is lower alkyl or R_2 and R_3 together form a divalent amino protecting group,

wherein the process comprises the steps of:

d) treating Z/E mixture of a compound of Formula I having unwanted E-isomer with one or more amines, wherein R is hydrogen or a metal cation capable of forming a salt;

e) adding one or more salt forming agents; and

f) isolating a Z-enriched compound of Formula I.

2. The process of claim 1, wherein the one or more amines are selected from compounds of Formula $NR_4R_5R_6$, wherein R_4, R_5 and R_6 are independently hydrogen, C_{1-6} straight or branched

chain alkyl, C_{3-10} single or fused ring cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, or independently R_3, R_4 and R_5 combine with each other to form a C_{3-7} cycloalkyl or heterocyclic residue comprising one or more heteroatoms selected from S, N or O.

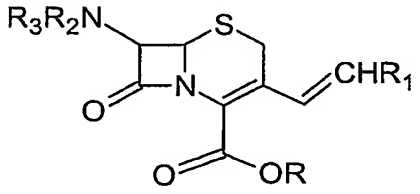
3. The process of claim 2, wherein the one or more amines are selected from methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, cyclopropylamine, cyclobutylamine, cyclopentylamine, cyclohexylamine, dicyclohexylamine, cycloheptylamine, aniline, N-methylaniline, N,N-dimethylaniline, p-toluidine, p-nitroaniline, diphenylamine, morpholine, N-methylmorpholine, piperazine, piperidine, N-methylpiperidine, pyrrolidine, N-methylpyrrolidine, N-methylpiperazine or mixtures thereof.

4. The process of claim 1, wherein the one or more salt forming agents are selected from sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium methoxide, sodium ethoxide, sodium 2-ethylhexanoate, potassium hydroxide, potassium carbonate, potassium t-butoxide, potassium acetate or mixtures thereof.

5. The process of claim 1 further comprising converting the Z-enriched compound of Formula I to its pharmaceutically acceptable ester by treating the Z-enriched compound of Formula I with one or more compounds of Formula R-L, wherein R comprises a C_{1-10} alkyl, 1-alkanoyloxyalkyl, 1-alkoxycarbonyloxyalkyl, cycloalkyl, cycloalkyloxy or C_{1-10} alkoxy and L is a leaving group.

6. The process of claim 5, wherein the one or more compounds of Formula R-L are selected from iodomethyl pivalate, bromomethyl pivalate, acetoxyethyl bromide, cyclohexyloxycarbonate, cyclohexyloxy-1-methylethylcarbonate or mixtures thereof.

7. A process for depleting E-isomers of a 3-(2-substituted vinyl)cephalosporin compound of Formula I from a Z/E mixture thereof,

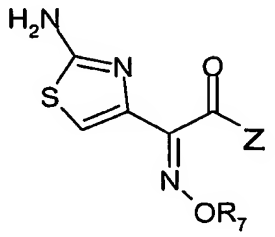


FORMULA I

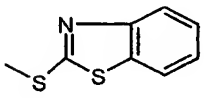
wherein the process comprises the steps of:

a) reacting a Z/E/ mixture of a compound of Formula I, wherein R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt, with one or more compounds

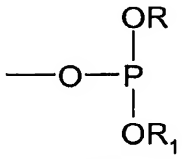
of Formula II, wherein Z is selected from a group having Formula IIa, IIb, IIc, IId,; and R, R_2 and R_3 are independently hydrogen,



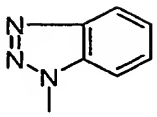
FORMULA II



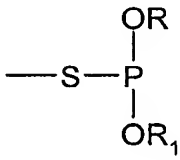
FORMULA IIa



FORMULA IIb



FORMULA IIc



FORMULA IId

f) optionally isolating a Z/E mixture of a compound of Formula I, wherein one of R_2 and R_3 is hydrogen and the other of R_2 and R_3 is a group of Formula A, wherein R_7 is lower alkyl;

g) optionally treating the product obtained in step a) or b) with one or more amines;

h) adding one or more salt forming agents; and

i) isolating the Z-enriched compound of Formula I.

8. The process of claim 7, wherein the one or more compounds of Formula II are selected from 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, benzotriazol-1-yl ester; 2-methoxyimino-2-(2-aminothiazol-4-yl)acetic acid, S-2-benzothiazole ester; 2-methoxyimino-2-(2-aminothiazol-4-yl)acetic acid, dialkylphonate ester or diarylphosphonate ester; 2-methoxyimino-2-(2-amino

thiazol-4-yl)acetic acid, dialkylphosphothionate ester, diarylphosphothionate ester or mixtures thereof.

9. The process of claim 7, wherein the Z/E mixture of a compound of Formula I is isolated in step b).

10. The process of claim 7, wherein the one or more amines are selected from compounds of Formula $NR_4R_5R_6$, wherein R_4, R_5 and R_6 are independently selected from hydrogen, C_{1-6} straight or branched chain alkyl, C_{3-10} single or fused ring cycloalkyl, optionally substituted aryl, optionally substituted aralkyl or independently R_3, R_4 and R_5 combine with each other to form a C_{3-7} membered cycloalkyl or heterocyclic residue containing one or more heteroatoms selected from S, N or O.

11. The process of claim 10, wherein the amine is selected from methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, cyclopropylamine, cyclobutylamine, cyclopentylamine, cyclohexylamine, dicyclohexylamine, cycloheptylamine, aniline, N-methylaniline, N,N-dimethylaniline, p-toluidine, p-nitroaniline, diphenylamine, morpholine, N-methylmorpholine, piperazine, piperidine, N-methylpiperidine, pyrrolidine, N-methylpyrrolidine, N-methylpiperazine or mixtures thereof.

12. The process of claim 7, wherein salt forming agent is selected from sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium methoxide, sodium ethoxide, sodium 2-ethylhexanoate, potassium hydroxide, potassium carbonate, potassium t-butoxide, potassium acetate or mixtures thereof.

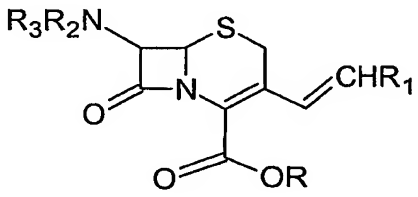
13. The process of claim 7 further comprising converting the Z-enriched compound of Formula I to its pharmaceutically acceptable ester by treating the Z-enriched compound of Formula I with one or more compounds of Formula R-L, wherein R comprises an alkyl, 1-alkanoyloxyalkyl, 1-alkoxycarbonyloxyalkyl, cycloalkyl, cycloalkyloxy or alkoxy, having 1 to 10 carbon atoms and L is a leaving group.

14. The process of claim 13, wherein the one or more compounds of Formula R-L are selected from iodomethyl pivalate, bromomethyl pivalate, acetoxyethyl bromide, cyclohexyloxycarbonate, cyclohexyloxy-1-methylethylcarbonate or mixtures thereof.

15. The process of claim 7, wherein the reaction of step a) is carried out in the presence of one or more bases, wherein the one or more bases are selected from one or more inorganic compounds or one or more organic salts.

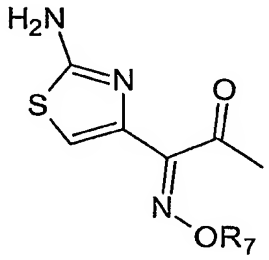
16. The process of claim 15, wherein the one or more bases are selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, aluminum hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium methoxide, potassium t-butoxide, sodium ethoxide, triethylamine, dicyclohexylamine, diphenylamine or mixtures thereof.

17. A Z-enriched compound of Formula I,



FORMULA I

wherein R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt; R_1 is hydrogen or a 5, 6 or 7 membered heterocyclic residue containing one more heteroatoms selected from N, S or O, halo, substituted C_{1-8} alkyl, aryl, aralkyl, or SR_6, wherein R_6 is straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl, or a heterocyclic residue; and R_2 and R_3 are independently hydrogen, monovalent amino protecting group or a group of Formula A,



FORMULA A

wherein R_7 is lower alkyl or R_2 and R_3 together form a divalent amino protecting group, comprising less than 5% of unwanted E-isomer.

18. The Z-enriched compound of Formula I of claim 17 comprising less than 2 % E-isomer.

19. The Z-enriched compound of Formula I of claim 17 comprising less than 0.5% E-isomer.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/000984

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D501/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2005	08/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lauro, P

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